IMMUNOSUPPRESSIVE DRUGS: SCIENTIFIC PRINCIPLES OF DEVELOPING COMBINATION DOSAGE FORMS

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Relevance: Immunosuppressant drugs are among the key therapeutic groups in modern transplantology and the treatment of autoimmune diseases. These agents suppress the immune response by inhibiting lymphocyte proliferation, limiting cytokine synthesis, or blocking intracellular signaling pathways. As a result, they prevent graft rejection and alleviate the course of chronic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis.

However, the use of immunosuppressants as monotherapy in clinical practice is associated with a number of challenges: administration at high doses often leads to severe adverse effects, including nephrotoxicity, hepatotoxicity, hematological disorders, and metabolic syndrome; long-term use of certain agents increases susceptibility to infections; pharmacokinetic variability (e.g., reduced absorption when taken with food, genetic differences in metabolism) directly affects therapeutic efficacy.

To address these issues in clinical practice, various immunosuppressants are prescribed in combination. For example, tacrolimus + mycophenolate mofetil, cyclosporine + azathioprine, and tacrolimus + everolimus are commonly used combinations. Nevertheless, the simultaneous administration of several drugs is inconvenient for patients, reduces treatment adherence, and complicates the monitoring of drug–drug interactions. Therefore, the development of fixed-dose combination dosage forms — such as tablets or capsules containing multiple active substances — represents a highly relevant direction in pharmaceutical technology.

Materials and methods: The study included literature analysis, generalization of clinical practice data, and comparative assessment of pharmaceutical technologies. The main manufacturing methods of combination tablets (wet granulation, dry granulation, direct compression) were evaluated. The physicochemical compatibility of active substances, their interaction with excipients, solubility, and disintegration properties were studied. Critical quality attributes such as dose uniformity, mechanical strength, dissolution, and disintegration were comprehensively assessed.

Results: The research led to the following scientific and practical conclusions: Pharmacodynamic synergy - the combination of immunosuppressants acting through different mechanisms (for example, mycophenolate mofetil, a purine synthesis inhibitor, and tacrolimus, a calcineurin inhibitor) allows achieving higher clinical efficacy at lower doses. Reduction of adverse effects - in combination forms, the dose of active substances is reduced, which significantly decreases the incidence of nephrotoxicity, hematological disorders, and infectious complications. Pharmacokinetic stability - a fixed-dose formulation harmonizes the rate and duration of drug absorption, maintaining stable plasma concentrations without sharp fluctuations. Clinical convenience - a single combination tablet simplifies the administration process for patients, improves adherence to therapy, and strengthens treatment effectiveness. Technological opportunities - in the development of combination forms, wet granulation was evaluated as the most optimal method, as it

ensures uniform distribution of substances, while coating technologies provide the possibility to regulate the release rate of active ingredients.

Conclusions: The development of combination immunosuppressive dosage forms is a promising approach to improve the treatment of transplantation and autoimmune diseases. Such formulations can increase therapeutic efficacy, minimize adverse effects, and enhance patients' quality of life. In this context, creating a combination tablet based on mycophenolate mofetil constitutes a highly relevant scientific and practical task for both the pharmaceutical industry and the healthcare system.